HEXITOL COMPOSITIONS AND USES THEREOF

This application claims the benefit of U.S. Provisional Application No. 60/208,644, filed June 1, 2000.

FIELD OF THE INVENTION

The technical field of the invention is the use of hexitols with antiproliferative agents to treat a host with a cellular proliferative disease.

BACKGROUND OF THE INVENTION

There is considerable interest in modulating the efficacy of currently used antiproliferative agents to increase the rates and duration of antitumor effects associated with conventional antineoplastic agents.

Conventional antiproliferative agents used in the treatment of cancer are broadly grouped as chemical compounds which (1) affect the integrity of nucleic acid polymers by binding, alkylating, inducing strand breaks, intercalating between base pairs or affecting enzymes which maintain the integrity and function of DNA and RNA; (2) chemical agents that bind to proteins to inhibit enzymatic action (*e.g.*, antimetabolites) or the function of structural proteins necessary for cellular integrity (*e.g.*, antitubulin agents). Other chemical compounds that have been identified to be useful in the treatment of some cancers include drugs which block steroid hormone action for the treatment of breast and prostate cancer, photochemically activated agents, radiation sensitizers and protectors.

Of special interest to this invention are those compounds that directly affect the integrity of the genetic structure of the cancer cells. Nucleic acid polymers such as DNA and RNA are prime targets for anticancer drugs. Alkylating agents such as nitrogen mustards, nitrosoureas, aziridine containing compounds directly attack DNA. Metal coordination compounds such as cisplatin and carboplatin similarly directly attack the nucleic acid structure resulting in lesions that are difficult for the cells to repair which, in turn, can result in cell death. Other nucleic acid affecting compounds include anthracycline molecules such as doxorubicin, which intercalates between the nucleic acid base pairs of DNA polymers, bleomycin which causes nucleic acid strand breaks, fraudulent nucleosides such as pyrimidine and purine nucleoside analogs which are inappropriately incorporated into nucleic polymer structures and ultimately cause premature DNA chain termination. Certain enzymes that affect the integrity and functionality of the genome can also be inhibited in cancer cells by specific chemical agents and result in cancer cell death. These include enzymes that affect ribonucleotide reductase (*e.g.*, hydroxyurea, gemcitabine), topoisomerase I (*e.g.*, camptothecin) and topoisomerase II (*e.g.*, etoposide).

One of the most broadly used of these DNA targeted anticancer drugs is cisplatin (cis-diamminedichloroplatinum II, CDDP). This compound is active against several human cancers including testicular, small-cell lung, bladder, cervical and head and neck cancer.

While the clinical activity of cisplatin against these forms of cancers are demonstratable, improvements in tumor response rates, duration of response and ultimately patient survival are still sought. The invention described herein demonstrates the novel use of the hexitols and derivatives, including dianhydrogalactitol, which can potentiate the antitumor effects of chemotherapeutic drugs, in particular, agents affecting the integrity of nucleic polymers such as DNA. Hexitols, in particular galactitol (1,2:5,6-dianhydrogalacti-tol) represent unique structures when compared to the currently approved antineoplastic

agents. These open sugar structures are highly water soluble with highly reactive epoxide groups, also unique among functional groups currently exploited for antiproliferative or cytotoxic properties.

SUMMARY OF THE INVENTION

Methods and compositions are provided for the treatment of a host with a cellular proliferative disease, particularly a neoplasia. In the subject methods, a pharmaceutically acceptable hexitol and an antiproliferative agent are administered in an amount sufficient to modulate the cellular proliferative disease.

DETAILED DESCRIPTION OF THE FIGURES

Figure 1 depicts the general structure of a hexitol analog. R_1 and R_2 represent substitution groups.

Figure 2 depicts the structure of the hexitol analog, Dianhydrogalactitol.

Figure 3 shows tumor growth delay, as tumor volume on days after treatment with the hexitol analog, Dianhydrogalactitol (DAG), after treatment with cisplatin (CDDP), or after treatment with Dianhydrogalactitol followed by cisplatin.

DETAILED DESCRIPTION OF THE INVENTION

Methods and compositions are provided for the treatment of a host with a cellular proliferative disease, particularly a neoplasia. In the subject methods, a pharmaceutically acceptable hexitol is administered, preferably systemically, in conjunction with an antiproliferative agent to improve the anticancer effects. In a preferred embodiment, the hexitol provides a chemopotentiator effect.

The agents are provided in amounts sufficient to modulate a cellular proliferative disease. In one embodiment, modulation of a cellular proliferative disease comprises a reduction in tumor growth. In another embodiment, modulation of a disease comprises inhibition of tumor growth. In another embodiment, modulation of a cellular proliferative

disease comprises an increase in tumor volume quadrupling time (described below). In another embodiment, modulation of a cellular proliferative disease comprises a chemopotentiator effect. In another embodiment, modulation of a disease comprises a chemosensitizing effect. In other embodiments, modulation of a disease comprises cytostasis. In still other embodiments, modulation of a disease comprises a cytotoxic effect.

A chemical agent is a "chemopotentiator" when it enhances the effect of a known antiproliferative drug in a more than additive fashion relative to the activity of the chemopotentiator or antiproliferative agent used alone. In some cases, a "chemosensitizing" effect may be observed. This is defined as the effect of use of an agent that if used alone would not demonstrate significant antitumor effects but would improve the antitumor effects of an antiproliferative agent in a more than additive fashion than the use of the antiproliferative agent by itself.

As used herein, the term "hexitol" includes all members of that chemical family including dianhydrogalactitol and analogs thereof. The hexitol family is defined by chemical structure as depicted in Figure 1.

A hexitol analog is further defined but not limited to substituent changes in R1 and R2 (Figure 1). Examples of R_1 and R_2 substituents include hydrogen, hydroxyl, alkyl groups having a carbon chain length of from one to five carbons (C_{1-5}), amino groups, alkyl amine of chain length of from one to five carbons (C_{1-5}), and alkoxy with carbon chain length of from one to five carbons. In a preferred embodiment, a hexitol analog has the structure of dianhydrogalactitol, shown in Figure 2, where R_1 and R_2 are hydroxyl.

A specific example of hexitol is dianhydrogalactitol which is also known by the following chemical synonyms: Dianhydrodulcitol; Dulcitol diepoxide; DAD; DAG; 5,6-Diepoxydulcitol; 1,2:5,6-Dianhydrodulcitol; 1,2:5,6-Dianhydrogalactitol; 1,2:5,6-Diepoxydulcitol (Figure 2).

As used herein, antiproliferative agents are compounds which induce cytostasis or cytotoxicity. "Cytostasis" is the inhibition of cells from growing while "cytotoxicity" is defined as the killing of cells. Specific examples of antiproliferative agents include: antimetabolites, such as methotrexate, 5-fluorouracil, gemcitabine, cytarabine, pentostatin, 6-mercaptopurine, 6-thioguanine, L-asparaginase, hydroxyurea, N-phosphonoacetyl-L-aspartate (PALA), fludarabine, 2-chlorodeoxyadenosine, and floxuridine; structural protein agents, such as the vinca alkaloids, including vinblastine, vincristine, vindesine, vinorelbine, paclitaxel, and colchicine; agents that affect NF-κB, such as curcumin and parthenolide; agents that affect protein synthesis, such as homoharringtonine; antibiotics, such as dactinomycin, daunorubicin, doxorubicin, idarubicin, bleomycins, plicamycin, and mitomycin; hormone antagonists, such as tamoxifen and luteinizing hormone releasing hormone (LHRH) analogs; nucleic acid damaging agents such as the alkylating agents mechlorethamine, cyclophosphamide, ifosfamide, chlorambucil, dacarbazine, methylnitrosourea, semustine (methyl-CCNU), chlorozotocin, busulfan, procarbazine, melphalan, carmustine (BCNU), lomustine (CCNU), and thiotepa, the intercalating agents doxorubicin, dactinomycin, daurorubicin and mitoxantrone, the topoisomerase inhibitors etoposide, camptothecin and teniposide, and the metal coordination complexes cisplatin and carboplatin.

Any suitable dosage may be administered in the methods of the present invention. The dosage administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular compound and its mode and route of administration; the age, health, or weight of the subject; the nature and extent of symptoms; the metabolic characteristics of the drug and patient, the kind of concurrent treatment; the frequency of treatment; or the effect desired. Preferably, the maximum dosages administered for each drug are one half (½) the applicable LD_{50}, more preferably one third (1/3) the

applicable LD_{50}, and still more preferably one fourth (1/4) the applicable LD_{50}

In one embodiment, hexitols of the invention are administered at a dosage of between 0.2 mg/kg and 20 mg/kg. In a preferred embodiment, the administration of hexitols is at a dosage of between 0.5 mg/kg and 15 mg/kg. In a more preferred embodiment, the dosage is between 0.5 mg/kg and 10 mg/kg. In an even more preferred embodiment, the hexitols are administered at a dosage of between 1 mg/kg and 5 mg/kg.

The antiproliferative agents of the invention also may be administered within a range of suitable dosages. For example, cisplatin may be administered at a dosage between 0.2 mg/kg and 7.5 mg/kg. More preferably, cisplatin is administered at a dosage between 0.5 mg/kg and 5 mg/kg. Even more preferably, cisplatin is administered at a dosage between 1 mg/kg and 4 mg/kg.

The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1: **The Chemopotentiation of Cisplatin by Dianhydrogalactitol**

Transplantable experimental murine fibrosarcomas ($2x10^5$ RIF-1 cells) were grown intradermally in the flanks of 3 month old female C3H mice (Charles River, Hollister, CA). When the tumors reached a volume of approximately $100mm^3$, the mice were randomly assigned to each experimental group (4 mice per group).

The experimental compositions were prepared as described in Table 1.

TABLE 1

Agent	Dose	Solvent	Supplier
Dianhydrogalactitol	10 mg/kg	DMSO	NCI
Cisplatin	4 mg/kg	Water for injection	David Bull Labs

Dianhydrogalactitol was obtained from NCI and was made to the appropriate concentration in DMSO. Cisplatin (David Bull Laboratories- Mulgrave, Australia, lot. 5201844x) was made to the appropriate concentration in water for injection. The compositions were injected systemically (i.e., intraperitoneally, i.p.), in a volume of 100 microliters. For the treatment of group 3, dianhydrogalactitol, was injected 30 minutes prior to the injection of cisplatin. After treatment, the growth of the tumors was monitored three times per week by caliper measurements of three perpendicular diameters of the tumor and calculation of tumor volume from the formula:

$$V = \pi/6 \times D_1 \times D_2 \times D_3,$$

where D_{1-3} are the diameters in mm of the three perpendicular axes.

It should be noted that the injected volume of drug may be altered depending on the size of animal to be injected, in order to deliver the indicated dosage. For example, injection of larger animals will require that a larger amount of drug be delivered, and consequently, may require a larger volume for injection. Appropriate concentrations of drug for delivery can be readily determined using routine methods.

The tumors were followed until they reached a size of four times their day zero treatment volume (TVQT), or up to 30 days after treatment, whichever came first. The data is expressed as the "tumor volume quadrupling time" (TVQT) mean and as the "delay." Mean TVQT is the mean days required for individual tumors to grow to four times the tumor volume at the initial treatment day. The "delay" is the median of days required for a tumor to grow to four times the mean size of the treated group, minus the median of days required to grow to four times the mean size of the control group. The data is also expressed as the ratio of the tumor volume quadrupling time of the treated tumor over the untreated control group (TVQT/CTVQT). Increasing values of this ratio indicate increased antitumor response. The data is presented in Table 2 below and in Figure 3.

TABLE 2

Group	Treatment	Dose (mg/kg)	Mean TVQT ± S.E.	TVQT/CTVQT	Median (TVQT)	Delay (Days)
1	Untreated Control	-	6.3 ± 0.3	1.0	6.3	0.00
2	Dianhydrogalactitol	10	10.9 ± 0.8	1.7	11.4	5.12
3	Dianhydrogalactitol → Cisplatin	10 → 4	14.6 ± 0.7	2.3	14.9	8.65
4	Cisplatin	4	7.4 ± 0.3	1.2	7.7	1.45

The arrow (→) in Group 3 indicates administration 30 minutes following administration of Dianhydrogalactitol.

The results of Table 2 indicate that the antiproliferative activity of cisplatin is enhanced by the use of dianhydrogalactitol in that a more than additive effect was observed when both compounds were used to treat the tumor bearing mice (group 3) in comparison to the use of cisplatin alone (group 4) or dianhydrogalactitol alone (group 2).